

Abuse of Selected Psychoactive Stimulants: Overview and Future Research TrendsBahaa-eldin E. A. Rahim¹, Rashad Alsanosi², Umar Yagoub¹, M.S. Mahfouz³ and Yahya M. Solan⁴¹Medical Research Center, Jazan University, Kingdom of Saudi Arabia²Substance Abuse Research Center, Jazan University, Kingdom of Saudi Arabia³Department of Family & Community Medicine, Faculty of Medicine, Jazan University, Kingdom of Saudi Arabia⁴Administration of Primary Healthcare, Directorate of Jazan Health Affairs, Jazan, Kingdom of Saudi Arabia
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Abstract: To date, a large and growing body of research has addressed the effect of various substances abuse from different medical and clinical psychological aspects. However, research on the behavioral and cognitive effects of abusing of particular psycho-stimulants including Khat, non-prescribed amphetamine and rejuvenated method of tobacco smoking i.e. waterpipe (shisha) on human subjects is not that extensive. This review aimed at gathering recent scientific literature on addiction influence of selected psychoactive substances (namely Khat, tobacco and amphetamine) to human and community health. Considerable research studies have been done so far on prevalence of Khat chewing and effects of tobacco (mainly on cigars smoking) highlighting the addictive nature and associated health problems. On contrast, there is a substantial knowledge gap regarding the neurobehavioral effects of non-prescribed amphetamine drugs and amphetamine-type stimulant (Khat) on human neurobehavioral performance which in turn might shed the light on themes for future research trends. The literature reports that the prevalence of these substances is alarmingly high among nations of Arab and African horn as a part of their cultural and habitual behavior. However due to the recent scattering of these nations worldwide, the issue of these substances becomes of global concern. The review attempts to extract lessons learned from previous studies and briefly summarized various aspects of the medical and psychological effects of using such stimulants on human health with much emphasis on cognitive and behavioral deficits. Chemistry, toxicity, general pharmacology of the reviewed psycho-stimulants together with the lessons learned and associated future research trends are also presented.

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1. Introduction

Substance abuse usually denotes to substances that associated with psychoactive but non-therapeutic drugs or chemical substances that lead to dependence syndrome and alter mental functioning (WHO 2011; Health Officers Council of British Columbia 2005).

The terms “drug abuse”, “drug addiction” and “drug dependence” are widely considered scientifically synonymous and been used as a technical term in the medical literature. However drug addiction has been used mainly for drug abuse to provide a more general level of information to the public. On contrast, the term “drug habit” is thought to be a psychological dependence rather than a physical dependence, and it is not thought to create the same damage to society as drug abuse (Health Officers Council of British Columbia, 2005; WHO 2004; Benowitz, 1999; US Department of Health and Human services, 1988). Table 1 summaries the main criteria associated with substance abuse.

The use or abuse of addictive substances, namely Khat (*Catha edulis*, *Celastraceae*), tobacco (cigars and waterpipe), and recently amphetamine is

the major socio-medical issue that threatens the community peace worldwide. This phenomenon becomes a tradition to region of the Middle East, African Horn nations and some parts of central Asia. Cigarette smoking is a serious health problem and most important avoidable causes of death in world (Council of The European Union, 2011; UNODC 2010; Ali 2007; Carrier, 2007; Tesfaye et al., 2006; Gelaw and Haile-Amlak, 2004; Drake, 1988; Kennedy, 1987). During a Khat session, other psychoactive and addictive substances including Arabic coffee, light tea and tobacco (water pipe or cigarettes) are provided. Smoking has been strongly implicated as a risk factor for chronic obstructive pulmonary disease, cancer and atherosclerosis, etc. (Khan and Malhotra, 2011; Pasupathi et al., 2009). Khat plant (Figure 1) grows wild in countries bordering the Red Sea and along the east coast of Africa. It's an evergreen shrub, which is cultivated as a bush or small tree. The leaves have an aromatic odor.

The taste is astringent and slightly sweet. The plant is seedless and hardy, growing in a variety of climates and soils. Khat can be grown in droughts

where other crops have failed and also at high altitudes (Glenice and Hagen, 2003). Khat chewing (also pronounced "Takhzeen") is a common deep-rooted socio-cultural traditional habit among nations of African Horn and southwest of Arabia Peninsular. Such habit aims at attaining a state of euphoria and stimulation.

Table 1. Criteria for Drug Abuse/Dependency

<p>Primary criteria</p> <ul style="list-style-type: none"> ▪ Highly controlled or compulsive use ▪ Psychoactive effects ▪ Drug-reinforced behaviour <p>Additional criteria</p> <ul style="list-style-type: none"> ▪ Addictive behaviour often involves: <ul style="list-style-type: none"> ○ Stereotypic patterns of use ○ Use despite harmful effects ○ Relapse following abstinence ○ Recurrent drug cravings <p>Dependence-producing drugs often produce:</p> <ul style="list-style-type: none"> ▪ Tolerance ▪ Physical dependence ▪ Pleasant (euphoriant) effects

Source: US Department of Health and Human services. 1988

The habit involves picking tender leaves of Khat, inserting them into one side of the mouth, chewing them for a while and storing them in the same side of the mouth. Khat is a green leafy shrub that acts as a mild stimulant when chewed. The Khat tree grows abundantly in Yemen, where Khat is legal. It is commonly consumed by Yemeni expatriates in Saudi Arabia, being smuggled from Yemen. Many Saudis also visit Yemen with the purpose of consuming Khat. Yet, Khat is cultivated as well in the Saudi Arabian part of the Yemeni border (Jazan), where locals consider it as a part of their daily lives and culture. Hence, the authorities have been implementing a different approach for controlling the use of Khat based more on persuasion and information campaigns rather than prosecution (Council of The European Union, 2011). Yemenis also use Khat for sociologic and anthropologic reasons described in detail in early works (Chaouachi, 2007). One of the major findings of these studies in the field of social sciences shows that the use of the mada'a is a chief element of the ritual Khat parties that take place during the long afternoons in Yemen.

Cigarette smoking is powerfully addictive, and caused 100 million deaths in the 20th century. In the 21st century, if smoking trends persist as expected, one billion people will die from smoking tobacco (Royal College Physicians, 2007). The World Health Organisation Study Group on Tobacco Product Regulation (TobReg) has issued in 2005 an



Figure 1. A bundle of Khat (*Catha edulis*) (Modified after Al-Motarreb et al 2010)

"Advisory Note" entitled: "Waterpipe Tobacco Smoking: Health Effects, Research Needs and Recommended Actions by Regulators". "Waterpipe" smoking is now considered a global public health threat and the corresponding artefact is actually known in the world under three main terms: hookah, narghile and shisha (Chaouachi, 2006). Figure 2 illustrates a cross-sectional view of a water-pipe device.

Fenethylamine, commonly known by the trademark name 'captagon', is one of the most popular drugs of abuse among the young affluent communities of the Middle East (Mahmoud, 2005). The most common drugs in Saudi Arabia are hashish and amphetamines. Hashish comes mainly from Afghanistan, Pakistan, UAE and Yemen. The amphetamines are mostly produced in Turkey, Syria and Jordan and usually come in the form of Captagon pills. Captagon was the brand name of fenethylamine, a synthetic stimulant used as a milder alternative to amphetamines before being banned in 1986 (Council of The European Union, 2011). Captagon is very common among students, especially before exams, because it is considered to enhance performance. For the same reason it is used by people employed in strenuous jobs, such as drivers, workers, etc. Captagon, being a member of the Amphetamine family, is trafficked into Turkey from eastern European countries; and shipped to Middle East and Arabic countries transiting Turkey. Captagon is not widely used in Turkey (TMCDDA 2008).

The main literature searches for this review were conducted during December 2011 using a number of search terms and bibliographic data sources including PubMed, Medical Database, sciencedirect.com, Taylor & Francis, Wiley-Online Library and published technical reports. In drawing together the evidence for this review we aimed to:

- i. understand the nature and extent of the problem for these selected addictive substances.
- ii. extract lessons from previous studies.

- iii. identify areas for future research studies with much emphasis on psychosis and neuropsychological effects of nicotine, amphetamine and amphetamine-type stimulants (ATS) on human health.

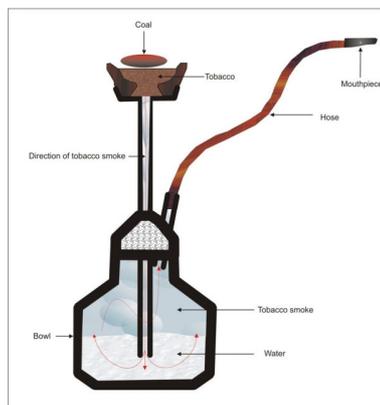


Figure 2. Water-pipe cross-sectional view

2. Prevalence

Khat is a psychostimulant plant used by over 10 million people daily, mainly in eastern Africa and the Middle East particularly southern of the Arab Peninsula where leaves of the Khat bush are widely used as a stimulant (Rashad et al., 2011; Al-Motarreb et al., 2010; Lukandu et al., 2008a; Date 2004; Brenneisen et al 1990). The major cultivation and production areas of Khat are in Ethiopia, particularly in Harar district, and in Yemen (Al-Hebshi and Skaug 2005). Global seizures of Khat were estimated at 106.9, 97.5 and 101.4 tons in 2004, 2005 and 2006, respectively (Griffiths et al., 2010). The habit of chewing Khat has prevailed for centuries among populations in the regions where it is grown (Reda et al 2012; Rashad et al 2011; Getahun et al 2010; Laswar and Darwish 2009). However, its use is gradually spreading to other parts of the world including Europe (Figure 3) and North America due to global migration (Griffiths et al., 2010; Lamina, S. 2010; El-Wajeh and Thornhill, 2009; Lukandu et al., 2009; Al-Hebshi and Skaug 2005; Mion, et al 1998).

Among other addictive substances, tobacco use especially in form of cigarette smoking remains highly prevalent all over the world (Royal College Physicians, 2007; United Nations 2005). The literature nowadays reports that the use or misuse of addictive substances, such as cigarettes and Khat is increasingly prevalent worldwide among male and females from different backgrounds in the Khat-origin countries (Rashad et al., 2011; Ageeli, 2009; World Bank, 2007; Tesfaye et al., 2006; Schoenmaker et al., 2005; Patel et al., 2005; Gelaw and Haile-Amlak, 2004; Rani et al.,

2003; Kalil, 2002; Tariq and Naseem, 2000; Griffiths, 1998).

Today waterpipe tobacco smoking is alertly emerging worldwide specially the Arabian Peninsula, Turkey, India and Pakistan (Abdullah and Naseem, 2011; Attia et al., 2010; Cobb et al 2010; Knishkowy and Amitai 2005).

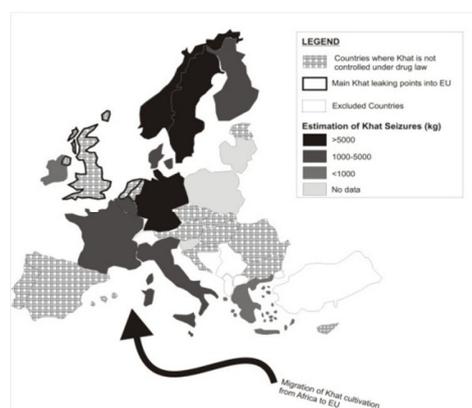


Figure 3. Countries among EU Member States and Norway not specifically controlling Khat under drugs laws, and estimates of Khat seizures. (Modified after Griffiths et al., 2010)

Narghile smoke contains toxicant inhalation at even greater levels than with cigarette does (Eissenberg et al., 2008). Water-pipe smoking recently has become the favorite form of tobacco use by youth globally specially the Eastern Mediterranean region (Akl et al., 2011; Sutfin et al., 2011; Dar-Odeh et al., 2010; Eissenberg et al., 2008; WHO 2005). While very few national surveys have been conducted, the prevalence of waterpipe smoking appears to be alarmingly high among school students and university students in Middle Eastern countries and among groups of Middle Eastern descent in Western countries. There is growing evidence that smoking tobacco through a waterpipe by youth and young adults is on the rise worldwide (Maziak 2011; Roskin and Aveyard 2009; Eissenberg et al., 2008; WHO 2005). Figures 4 and 5 illustrate the prevalence of waterpipe usage across the world corresponding to different age.

Marijuana, heroin, morphine or cocaine are the substances which come to mind first when the use or illegal trade of narcotics or stimulatory substances are thought. However, there are also some other active drug components such as amphetamine-type stimulants (ATS) possess psychoactive effects, are known to be used outside of their medical prescriptions (Asicioglu et al 2010).

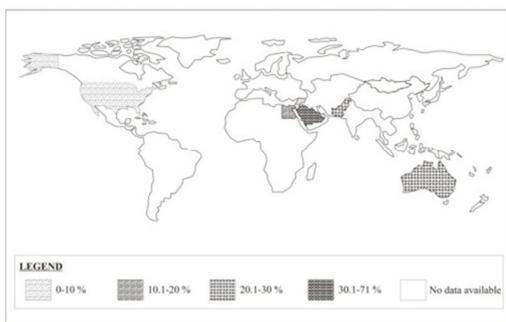


Figure 4. Waterpipe use among school students across the world (Modified after Akl et al., 2011)

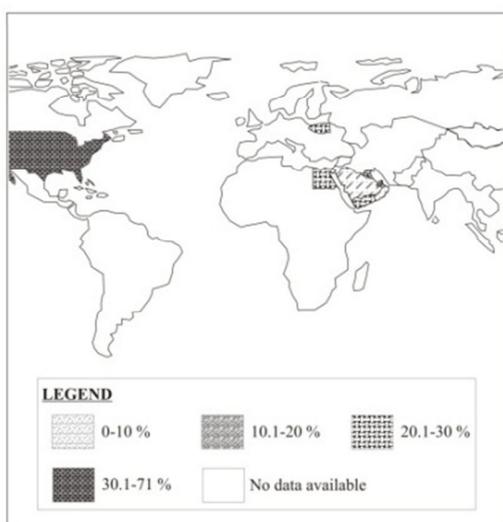


Figure 5. Waterpipe use among adult across the world (Modified after Akl et al., 2011)

Global seizures of amphetamine reached a record level of 23.7 tons in 2007, and essentially sustained this level in 2008, amounting to 22.9 tons. Amphetamine seizures remained concentrated in the Near and Middle East States and West and Central Europe (Table 2), which together accounted for 96 per cent of global seizures in 2008 in which Saudi Arabia is accounted for approximately 30% of all global amphetamine seizures (Council of The European Union, 2011). While drug seizures vary dramatically from year to year, clear increases in the amount of amphetamine seized began around 2000, with large increases reported in 2005. These increases are due, in large part, to interceptions of a fake pharmaceutical marketed as Captagon (amphetamine) in the Near and Middle East which in turn, enhanced the ATS market to rejuvenate in these areas (Figure 6).

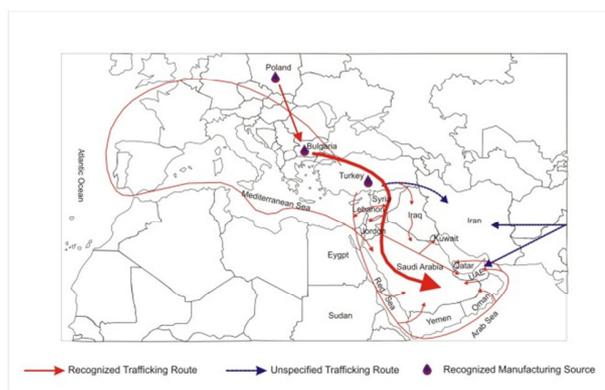


Figure 6. Road map of amphetamine manufacturing and trafficking. (Modified after UNODC, 2009)

Table 2. Global and regional drug seizures and seizure trends, 2007-2009

Stimulant ¹	2007		2008		Trend in NME	
	NME ² (Kg)	Global (Kg)	NME (Kg)	Global (Kg)	2007 - 2009 (%)	2007 - 2009 (%)
Amphetamine	15,065	23,750	14, 203	22,944	-6%	*
Methamphetamine	38	18,211	1,473	20,656	3775%	Increased
Non-defined Amphetamine	233	1,802	57	3,829	-75%	*
Ecstasy	119	7,937	104	3,860	-12%	Decreased

¹ Amphetamine-type stimulants are seized in various forms, including liquid and tablet form, and may be reported by mass, volume, number of tablets or other units.

²NME: Near and middle east region

*: Since data for 2009 were incomplete at the time of preparation of the present report, totals for 2009 are not presented in the table. The trend between 2008 and 2009 was assessed by comparing totals over 15 members of the NME states for which amphetamine-type stimulants' data were available for both 2008 and 2009, for 90 % or more of the total for 2008.

Source: UNODC (2010)

3. Chemistry

The chemistry of Khat is much dependent on climatological conditions. There are some 44 different types of Khat plant cultivated in different geographic areas across Yemen (Lamina 2010; Al Motarreb 2002; Geissshusler and Brenneisen 1987).

Among many different chemical compounds found within the manufactured cigarette, the main source of tobacco addiction is nicotine. Nicotine is a weak base with a pKa (index of ionic dissociation) of 8.0 which means that at pH 8.0, 50% of nicotine is ionized and 50% is non-ionized. Nicotine absorption across biological membranes depends on its pH (Benowitz, 1988; US Department of Health and Human services, 1988). The pH of smoke from flue-cured tobaccos found in most cigarettes is acidic (pH 5.5 to 6.0). At this range of pH, the nicotine is almost completely ionized, which means that the nicotine is barely absorbed when the smoke is held in the mouth. However, when tobacco smoke reaches the lung, nicotine is rapidly absorbed because of the huge surface of the alveoli in the lung and the higher pH of the fluid in the lung (approximately 7.4) compared with the mouth (Benowitz, 1999; US Department of Health and Human services, 1988; Gori et al 1986).

Amphetamines include Δ -amphetamine, L-amphetamine, ephedrine, methamphetamine, methylphenidate, and pemoline. Another member of this group is cathinone, the active ingredient in freshly gathered leaves of the Khat shrub (*Catha edulis*), whose actions are very similar to that of amphetamine. On the other hand, synthetic cathinones abuse (i.e. cathinone-based drugs) is considered somehow a growing proportion of the new psychoactive substances identified in Europe which in turn may suggest its significant potential for future diffusion (WHO 2004; Jaffe, 1990).

There are many different compounds found in Khat including alkaloids, terpenoids, flavonoids, sterols, glycosides, tannins, amino acids, vitamins and minerals (Aiman, 2009; El-Wajeh and Thornhill, 2009; Cox and Rampes 2003; Mion, et al 1998; Kalix et al., 1990; WHO 2004). The phenylalkylamines and the cathedulins are the major alkaloids. The Khat phenylalkylamines comprise cathinone [S(-)-cathinone], and the two diastereoisomers cathine [1S,2S-(+)-norpseudoephedrine or (+)-norpseudoephedrine] and norephedrine [1R,2S(-)-norephedrine]. These compounds are structurally related to amphetamine and noradrenaline (Coppola and Mondola. 2012; ACMD. 2010; EDCC, 2006).

3.1. Chemical formulae:

Cathinone: C₉H₁₁NO

Cathine and norephedrine: C₉H₁₃NO

Relative molecular mass (M_r):

Cathinone: 149.2

Cathine and norephedrine: 151.2

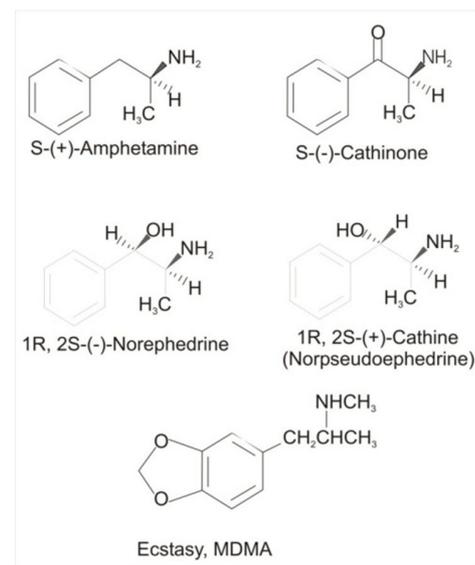


Figure 7. Chemical structures of amphetamine, cathine and cathinone

4. General Pharmacology

Khat contains more than 40 alkaloids, glycosides, tannins, amino acids, vitamins and minerals. Most of the effect of chewing Khat is thought to come from two phenylalkylamines – cathinone and cathine – which are structurally related to amphetamine (Cox and Rampes 2003). The main psychoactive compounds in Khat leaves are cathine and cathinone, which are some 2- to 10-fold less active than amphetamine (Pennings et al., 2008). The pleasure derived from Khat chewing is attributed to the euphoric actions of its content of (-)-S-cathinone, a sympathomimetic amine with properties described as similar to those of amphetamine (Kalix and Braenden 1985; Kalix 1988; Kalix 1992). Khat may severely influence the effectiveness of immune surveillance and anti-microbial capacity of PBMCs (Murdoch et al 2011).

5. Toxicity

Several cigarette brands are marketed as less harmful products and are erroneously advertised as “addiction-free cigarettes.” Examples of such products are “clove cigarettes” and the “American Spirit.” Smokers are being encouraged to switch to such products. Increasingly, these products are

popular among young smokers, but may be as dangerous as regular cigarettes (Tobacco.org. 2011). Health professionals must be aware of such industry tactics to correctly inform smokers of the nicotine content in these cigarettes and the addictive properties of the products. For example, clove cigarettes manufactured in Indonesia are believed to be safer than regular cigarettes (Malson et al 2003). In fact this is not true because clove cigarettes are composed of a mixture of tobacco (60% to 80%) and ground clove buds (20% to 40%) and thus still possess certain amounts of nicotine. Some literature demonstrates that 28 smoke yields from standardized machine-smoking analysis indicated clove cigarette products delivered more nicotine, carbon monoxide (CO), and tar than conventional cigarettes (Tobacco.org, 2011; Malson et al 2003; Sohn et al., 2003). Nicotine acts presynaptically to facilitate the release of neurotransmitters such as acetylcholine, norepinephrine, dopamine, beta endorphin, and serotonin-causing behavioral arousal and sympathetic neural activation (Sohn et al., 2003; Benowitz 1996; Benowitz 1992). Nicotine's effect on these neurotransmitters, which can mimic the pharmacologic effects of many antidepressants, have been implicated as a major component in the reinforcing effects of cigarette smoking, and the subsequent development of nicotine addiction. The neurotransmitters released by nicotine and their associated behavioral effects are presented in Table 3.

Table 3. Effects of Neurotransmitters enhanced by nicotine

Neurotransmitters	Effect
Dopamine	- pressure - Appetite suppression
Norepinephrine	- Arousal - Appetite suppression
Acetylcholine	- Arousal - Cognitive enhancement
Vasopressin	- memory improvement
Serotonin	- Mood modulation - Appetite suppression
Beta-Endorphin	- Reduction of anxiety and tension

Source: Benowitz 1999

Khat is genotoxic to cell within the oral mucosa, and several studies have suggested an association between Khat use and oral lesions like hyperkeratosis and oral cancer (Lukandu et al., 2008b). Cathine and cathinone are responsible for the desired psychogenic (suppression of hunger, mind stimulation, euphoria) and sympathicomimetic effects (Mion, et al 1998). Chronic toxicity of Khat is modest when used in low amounts, whereas at high levels, Khat use is associated with adverse effects,

like hypertension, heart rhythm disorders, insomnia and loss of appetite. In addition, Khat users show a higher prevalence of cancers in the digestive tract (Coppola and Mondola. 2012; Al-Motarreb et al 2010; Pennings et al., 2008). Khat is cytotoxic to peripheral blood mononuclear cells in a dose- and time-dependent manner and cell death was mediated by apoptosis (Murdoch et al 2011).

6. Medical and Psychological Effects on Human Performance

There is nowadays a handful of literature to suggest the harm impacts of addictive substances (Table 4) on different aspects of human health (Murdoch et al 2011; Köseoğlu et al., 2006; Verdejo-Garcia et al., 2004; Baker et al 2003; Rogers and Robbins, 2003; Tariq and Naseem, 2000). Khat use by untreated hypertensive patients who react strongly to vasoconstrictive effects can lead to hypertension and resulting cardiovascular complications (Mion, et al 1998; Hassan et al., 2000; Tesfaye 2006; Ali 2007; Shatoor et al 2011). Due to its serve impacts on human life, tobacco researches have been expended to understand the health consequences of cigarette smoking, both to the smoker and to nearby nonsmokers (Reno et al. 2011; Sharma and Vijayaraghavan 2008; Jha et al. 2008; Royal College of Physicians, 2007; Gupta et al. 1997; Church and Pryor, 1985). Harm ranking of the major psychoactive substance is presented in Figure 8.

6.1. Cognitive and behavioral deficits

There is a possible complex connection between the impact of tobacco use and influence of amphetamine-like of Khat use. Despite both nicotine and amphetamine are dopamine agonists, there are noticeable differences in their influence on behavioral measures. Observational and single-case studies are the most available researches investigated cognitive and behavioral impacts associated with Khat chewing in human. Obviously Khat chronic chewing habit associated with various mental and cognitive problems (Ersche et al., 2006; Ersche and Sahikian 2007; Odenwald, 2007; Odenwald et al., 2007; Balint et al., 2009; Odenwald et al., 2009).

Amphetamine has been associated with performance improvement on cognitive processes e.g. attention and psychomotor functioning. In contrast, it appears to impair performance in other areas of cognitive functioning, particularly those requiring ability to sieving out irrelevant information and/or visual scanning (Hoffman and Al'bsi 2010; Silber et al., 2006).

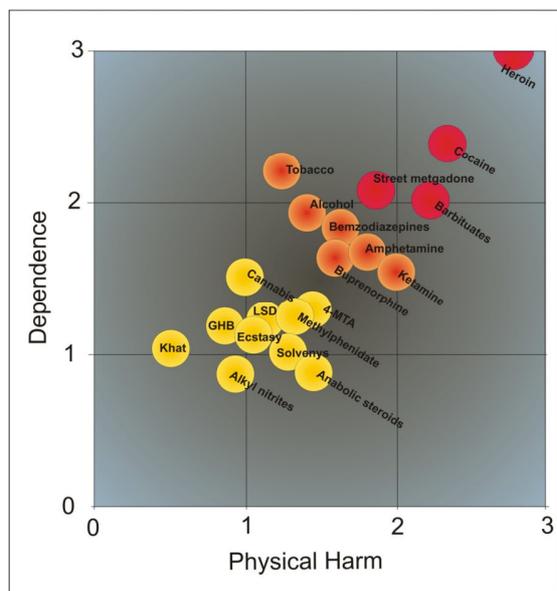


Figure 8. Rational scale to assess the harm of five drugs (Source: Nutt David et al., 2007)

6.2. Oral consequences

The association between Khat chewing and cigarette or water-pipe smoking may increase the risk of epithelial dysplasia (Tesfaye 2006; Ali 2007). Oral diseases reportedly associated with Khat chewing include periodontitis, oral leukoplakia and oral cancer (Lukandu et al., 2010; Rastam et al 2010; El-Wajeh and Thornhill, 2009; Fasanmada and Newman 2007). In recent a study (Faleh et al., 2007) the association of Khat chewing with the occurrence of oral cancer, the frequency of oral cancer among whole body cancers and the patients' histories of tobacco consumption and Khat chewing were examined in Yemen. the high relative frequency of oral SCC may be related to the habits of chewing tobacco and Khat. The association between tobacco smoke and periodontal diseases has been studied in a plethora of clinical and epidemiological investigations and many carcinogens such N-nitrosamines, aromatic amines, and polycyclic aromatic hydrocarbons are found in tobacco smoke (Smith et al., 2000; Smith et al., 1997; Bartsch et al., 2000). However it has been estimated that smoking accounts for half of all periodontal diseases (Tomar and Asma 2000). Tobacco in its many forms is a risk factor for oral cancer, periodontal disease, gingival recession, coronal, and root caries and oral mucosal lesions (in the case of smokeless tobacco).

Table 4. Characteristics of the selected psychoactive stimulants

Stimulant	Primary Mechanism Action	Behavioral Effect	Tolerance	Withdrawal	Prolonged use Effects
Nicotine	<ul style="list-style-type: none"> - Nicotinic cholinergic receptor agonist. - Increases sodium inflow through the channels, - Causing depolarization 	<ul style="list-style-type: none"> - Arousal, - Increased attention, concentration and memory - Decreased anxiety and appetite. - Stimulant-like effects 	<ul style="list-style-type: none"> - Tolerance develops through metabolic factors, as well as receptor changes. 	<ul style="list-style-type: none"> - Irritability, hostility, anxiety, dysphoria, depressed mood, decreased heart rate, increased appetite. 	<ul style="list-style-type: none"> - Health effects due to smoking well-documented. - Difficult to dissociate effects of nicotine from other tobacco components.
Amphetamines	<ul style="list-style-type: none"> - Increased release of dopamine from nerve terminals via dopamine transporter. - Not dependent upon action potentials. - Inhibits monoamine oxidase (MAO) 	<ul style="list-style-type: none"> - Increased alertness arousal, energy, motor activity, speech, self-confidence, concentration, feelings of well-being - Decreased hunger. - Increased heart rate. - Increased respiration, euphoria 	<ul style="list-style-type: none"> - Develops rapidly to behavioral and physiological effects 	<ul style="list-style-type: none"> - Fatigue - Increased appetite, irritability, emotional depression anxiety 	<ul style="list-style-type: none"> - Sleep disturbances - Anxiety - Decreased appetite - Increased blood pressure. - Decreased brain dopamine, precursors, metabolites and receptors

Source: WHO 2004

Moreover, tobacco adversely affects healing after periodontal treatment (Reno et al. 2011; Tariq and Naseem, 2000). While cigarette smoking is recognized as an important risk factor in human oral cancers (Reno et al. 2011; Royal College of Physicians, 2007; Sohn et al 2003; Tariq and Naseem, 2000; Carl et al 1995), the effect of water pipe smoking (WPS) on these cancers is not known (Khan and Malhotra, 2011; Rastam et al., 2010). It is possible that the co-morbidity of Khat and tobacco use poses higher risk than use of Khat alone on emotion regulation and cognitive functions.

Most of previous researches focused on the effects of addictive behaviors related to the co-morbidity of tobacco and other psychoactive substances use e.g. alcohol (John et al., 2003; Hurt and Patten, 2003) and marijuana use (Humfleet and Haas, 2004; Lai et al., 2000; Burns et al., 2000). Substance abuse behavior can be perceptively addressed in emergency departments via screening and delivery of brief intervention. Nonetheless, level of patients' readiness to change is not taken into account, and then such substance abuse interventions may not be efficient (Frausto and Bazargan-Hejazi 2009). Cigarette, waterpipe, Khat and amphetamine are psychoactive stimulants with the capacity to alter mood, cognition and behavior. Literature shows that students and workers like long distance drivers chew Khat to get the stimulant effect that improves performance, keeping them alert and increasing work capacity (Halbach, 1972; Kalix and Braenden, 1985; Zein, 1988; Toennes et al., 2003; Al-Habori, 2005). Khat chewing associated with various neurobehavioral impairments such as anorexia, weak stream of micturition, post-chewing urethral discharge and insomnia (delayed bedtime), which in turn result in late wake-up the following day, besides low work performance (Nageeb et al., 2002; Tesfaye et al., 2006). These effects are believed to be caused by the central and peripheral actions of cathinone and cathine in the Khat leaves (Smith-Simone et al. 2008). While psycho-social indicators of cigarette smoking (i.e. socio-demographic level, risk assessment, social norms, and pluralistic ignorance) were considered essential determinants of understanding smoking behavior, mainly among youth (DHHS, 1994; Flay, Petraitis, and Hu, 1999; Tariq and Naseem, 2000; Kobus, 2003; Tyas and Pederson, 1998), surprisingly, a few researches have investigated these factors in young adults, particularly those that are using alternative forms of tobacco such as waterpipe (Attia et al., 2010; Eissenberg et al 2008; Smith, 2006; Smith-Simone et al 2008). Nicotine is a potent and powerful agonist of several subpopulations of nicotinic receptors of the cholinergic nervous system and depends on dopamine for the behavioral effects that are most relevant for its reinforcing properties. This is likely to be the basis of the addictively-producing ability of tobacco. However, other neuronal systems related to

substance dependence, such as opioid, glutamate, serotonin and glucocorticoid systems may also be modulated by nicotine and may be of importance to specific aspects of substance dependence (Dani and De Biasi, 2001; Kenny and Markou, 2001; Malin, 2001). Nicotine results in some dose-related psycho-active effects in humans that are similar to those of addictive substances, and it elevates scores on comparatively standardized tests for liking and euphoria that are depended upon by WHO for evaluating addiction potential (Henningfield et al., 1996; Vidal, 1996; Paterson and Nordberg, 2000; WHO 2004).

Dependence to some psychoactive drugs such as methamphetamine causes slow performance in executive functions related to frontal lobe (Han et al., 2008) and weakened performance on the tests associated with ability of information manipulation, abstract thinking and perceptual speed (Simon et al., 2002). Patients are considered comorbid whenever reported any use of any synthetic substances including cocaine, opiates (illicit or illicitly obtained), marijuana, or (meth)amphetamine in the 30 days prior to admission or if their examined urine-positive for one of these synthetic drugs at admission. Major psychiatric diagnoses associated with (meth)amphetamine includes major depression, bipolar, other mood, schizoaffective, schizophrenia (Magura et al., 2009). Galloway et al (2008) hypothesize that subsequent methamphetamine use will decrease only when interventions relatively reduce the associated craving. Cognitive-behavioral therapy has a capable efficaciousness in elevating patients' confidence to resist craving to methamphetamine misuse (Hekmat et al. 2011; Yen et al 2004).

7. Lessons Learned

In order to design effective substance abuse control policy, it is essential to understand abusing prevalence and predictors. In the majority of cases, people use psychoactive substances because they expect to benefit from their use, whether through the experience of pleasure or the avoidance of pain. Reviewed literature has covered wide range of research topics associated mainly with neuro-cognitive deficit of chronic users of psychoactive substances including amphetamines and methamphetamines.

Careful screening of previous research studies addressed various addictive substances indicates an alarmingly increasing prevalence of nicotine addiction in the form waterpipe smoking in Arabic Peninsular and among Arab communities across the world. Despite the lethal ailments associated to shisha smoking, a little attention been paid to address its consequences. Underestimation of shisha health risks attributes mainly to the common misconceptions developed by users. This situation is made worse by the fact that Near- and

Middle-east regions account for > 90% of global amphetamine seizures in which Saudi Arabia alone accounts for approximately 30% of all global amphetamine seizures, which in turn paves the road for future substance abuse research studies pertaining to psychosis and neuropsychological effects of nicotine, amphetamine and amphetamine-type stimulants (ATS) and psychiatric comorbidity on, emphatically, Arab populations worldwide.

A vast body of evidence has proved that there is an adverse impairment in memory remarkably associated with chronic amphetamine and methamphetamine abuse. Pharmacologically, there is some correspondence between the active constituents (e.g. cathinone and cathine) of Khat and amphetamines; future studies therefore, should also vigilantly pay attention to examining the cognitive functioning (with much emphasis on the domains of learning, memory, and executive functions) in chronic Khat users and abstinent Khat users. In light of some common psychoactive characteristics of the reviewed substances, effects of addictive pleasurable combination of these psychoactive substances should be taken in account when extracting hypotheses for future studies tackling the neurobehavioral effects of Khat.

Reviewed literature indicates that waterpipe tobacco smoking involves toxicant inhalation at even greater levels than with cigarette smoking, nonetheless is notably increasing in prevalence which represents a growing public health issue. It has been noticed that due to lack and or absence of public health awareness, youth particularly in both Arabic countries and among Arab communities worldwide, have fallen back on shallow experiences to form views that waterpipe smoking is less harmful than other forms of smoking and it currently becomes much more common and acceptable in students communities than other forms of addictive substances.

Care should be taken in future research studies dealing with psychoactive substances to account for the co-morbidity or polystimulant use factor. Furthermore, more attention should be given to the perplexed factors of inadequate sample size and distribution as well as inappropriate variables of inclusion/exclusion criteria.

Knowledge gained from this literature should lead to greater understanding on the timing, duration, and extent to which specific risk and protective factors influence the outcomes of psychoactive substance use. In turn, findings from these studies shed the light for researchers on the road for future treatment and prevention studies.

Health decision-makers together with healthcare providers, campus supervisors, health instructors, religious guiders and educators, need not only to pay attention to conventional forms of tobacco smoking such as cigars but also to rejuvenated technique

of tobacco smoking such as waterpipe in order to establish more informed prevention, treatment, and policy strategies for tobacco control.

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References

1. Abdullah M, Al-Bedah, Naseem A. Qureshi. RE: Water pipe (shisha) smoking among male students of medical colleges in the eastern region of Saudi Arabia. *Ann Saudi Med.* 2011 Jan-Feb; 31(1): 94–95. DOI: 10.4103/0256-4947.75795.
2. ACMD. *Consideration of the cathinones*. Report prepared by Advisory Council on the Misuse of Drugs (ACMD). Available at: <http://www.namsdl.org/documents/ACMDCathinonesReport.pdf> (Downloaded on December 25th, 2011). 2010.
3. Aiman A A. Qat Habit in Yemen Society: A Causative Factor for Oral Periodontal. Diseases. *Int J Environ Res Public Health.* 2007; 4(3): 243–7.
4. Akl A Elie, Sameer K Gunukula, Sohaib Aleem, Rawad Obeid, Philippe Abou Jaoude, Roland Honeine, Jihad Irani. The prevalence of waterpipe tobacco smoking among the general and specific populations: a systematic review. *BMC Public Health.* 2011; 11: 244. DOI:10.1186/1471-2458-11-244.
5. Al-Habori M. The potential adverse effects of habitual use of *Catha edulis* (Khat). *Expert Opin Drug Saf.* 2005; 4(6): 1145-54.
6. Al-Hebshi NN, Skaug N. Khat (*Catha edulis*)—an updated review. *Addiction Biol.* 2005; 10: 299 – 307.
7. Ali, AA. Histopathologic changes in oral mucosa of Yemenis addicted to water-pipe and cigarette smoking in addition to takhzeen al-qat. *Oral surgery oral medicine oral pathology oral radiology and endodontics.* 2007, 103(3): e55-e59.
8. Al-Motarreb A, Al-Habori M, Broadley K.J. Khat chewing, cardiovascular diseases and other internal medical problems: The current situation and directions for future research. *Journal of*

- Ethnopharmacology*. 2010; 132(3): 540-548. doi:10.1016/j.jep.2010.07.001.
9. Al Motarreb A, Baker K, Broadley KJ. Khat: pharmacological and medical aspects and its social use in Yemen. *Phytother Res*. 2002; 16: 403-413.
 10. Attia Z Taha, Amr A Sabra, Zaid Z Al-Mustafa, Hasan R Al-Awami, Mujtaba A Al-Khalaf, Momen M Al-Momen. Water pipe (shisha) smoking among male students of medical colleges in the eastern region of Saudi Arabia. *Ann Saudi Med*. 2010; 30(3): 222-226. DDI: 10.4103/0256-4947.62838.
 11. Knishkowsky B, Amitai Y. Water-Pipe (Narghile) Smoking: An Emerging Health Risk Behavior. *Pediatrics*. 2005; 116(1): e113-e119. DOI: 10.1542/peds.2004-2173.
 12. Asicioglu F, Kucukibrahimoglu EE, Ilingi U. Psychotropic drugs evaluated in the context of narcotic drugs according to the new Turkish criminal law. *Bulletin of Clinical Psychopharmacology*. 2010; 20(4): 314-320.
 13. Baker A, Kay-Lambkin F, Lee NK, Claire M, Jenner L. *A Brief Cognitive Behavioural Intervention for Regular Amphetamine Users*. A Treatment guide. Australian Government Department of Health and Ageing. . Online ISBN 1-74186-504-2. 2003.
 14. Bartsch H, Nair U, Risch A, Rojas M, Wikman H, Alexandrov K. Genetic polymorphism of CYP genes, alone or in combination, as a risk modifier of tobacco-related cancers. *Cancer Epidemiol Biomarkers Prev*. 2000. 9(1): 3-28.
 15. Benowitz N. Nicotine addiction. *Prim Care*. 1999, 26: 611-631.
 16. Benowitz NL. Pharmacology of nicotine: Addiction and therapeutics. *Ann Rev Pharmacol Toxicol*. 1996; 36: 597-613.
 17. Benowitz NL. Cigarette smoking and nicotine addiction. *Med Clin North Am*. 1992; 76: 415-436.
 18. Benowitz N. Pharmacologic aspects of cigarette smoking and nicotine addiction. *N Engl J Med*. 1988; 319: 1318-1330.
 19. Brenneisen R, Fisch H-U, Koelbing U, Geissshusler S, Kalix P. Amphetamine-like effects in humans of the Khat alkaloid cathinone. *Br. J. clin. Pharmacol*. 1990; 30: 825-828.
 20. Burns CB, Ives RG, Lindorff KJ, Clough AR. Cannabis: a Trojan horse for nicotine? *Australian and New Zealand Journal of Public Health*. 2000; 24(6): 637. PMID: 11215017.
 21. California State Department of Health Services. *Scientific advisory board on clove cigarettes Health hazards of clove cigarettes*. A report to the legislature prepared pursuant to health and safety code section statutes of 1985, Berkeley, CA, Office of Environmental Health Hazard Assessment. *JAMA*. 1988; 260: 3641-3644.
 22. Carl MA, Vigneswaran N, Tilashalski K, Rodu B, Cole P. Tobacco use and cancer: A reappraisal. *Oral Surgery Oral Medicine, Oral Pathology, Oral Radiology and Endodontol*. 1995; 80(2): 178-182.
 23. Carrier NCM. *Kenyan Khat: The social Life of a Stimulant*. Koninklijke Brill NV, Leiden, The Netherlands. 2007.
 24. Cobb C, Ward KD, MaziK W, Shihadeh AL, Eissenberg T. Waterpipe Tobacco Smoking: An Emerging Health Crisis in the United States. *Am J Health Behav*. 2010; 34(3): 275-285. DOI: 10.1111/j.1360-0443.2011.03649.x.
 25. Chaouachi K. A critique of the WHO TobReg's "Advisory Note" report entitled: "Waterpipe tobacco smoking: health effects, research needs and recommended actions by regulators". *Journal of Negative Results in BioMedicine*. 2006; 5: 17. doi:10.1186/1477-5751-5-17.
 26. Chaouachi KT. Qat chewing and water pipe (mada'a) smoking in Yemen: a necessary clarification when studying health effects on oral mucosa. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontology*. 2007;104, (6): 731-733.
 27. Church D, Pryor WA. Free-radical chemistry of cigarette smoke and its toxicological implications. *Env. Health Persp*. 1990; 64: 111-126.
 28. Coppola M, Mondola R. 3,4-Methylenedioxypropylvalerone (MDPV): Chemistry, pharmacology and toxicology of a new designer drug of abuse marketed online. *Toxicology Letters*. 2012; 208 (1, 5): 12-15. doi:10.1016/j.toxlet.2011.10.002.
 29. Council of The European Union. *Regional Report on the Near East*. No. 5020/11 CORDROGUE 1. Brussels, Belgium. 2011.
 30. Cox G, Rampes H. Adverse effects of Khat: A review. *Adv Psychiatr Treatm*. 2003; 9: 456-463. doi: 10.1192/apt.9.6.456.
 31. Dani JA, De Biasi M. Cellular mechanisms of nicotine addiction. *Pharmacology, Biochemistry and Behavior*. 2001; 70: 439-446.
 32. Dar-Odeh NS, Faris GB, Mahmoud KA, Hamzeh MA, Hazem AE, Ameen SK, Shatha MK., Abdul-Aziz FD, Mohamed N, Samer M, Louai A, Osama AA. Narghile (water pipe) smoking among university students in Jordan: prevalence, pattern and beliefs. *Harm Reduction J*. 2010; 7(10):1-6.
 33. DHHS. Preventing tobacco use among young people: A report of the surgeon general. Atlanta, Georgia: DHHS/CDC/NCCDPHP/OSH. 1994.
 34. Date J, Noritoshi Tanida, Tatsuya Hobara. Qat chewing and pesticides: a study of adverse health effects in people of the mountainous areas of Yemen. *International Journal of Environmental Health Research*. 2004; 14(6): 405-414.

35. Drake PH. Khat-chewing in the Near East. *Lancet*. 1988; 1(8584): 532-3.
36. El-Wajeh YAM, Thornhill MH. Qat and its health effects. *British Dental Journal*. 2009; 206(1): 17-21.
37. ECCDD. *Assessment of Khat (Catha edulis Forsk)*. Document # ECDD 2006/4.4 . WHO Expert Committee on Drug Dependence (ECDD). 2006.
38. Eissenberg T, Ward KD, Smith-Simone S, Maziak W. Waterpipe Tobacco Smoking on a U.S. College Campus: Prevalence and Correlates. *Journal of Adolescent Health*. 2008; 42: 526–529. doi:10.1016/j.jadohealth.2007.10.004.
39. Ersche KD, Sahikian BJ. The Neuropsychology of Amphetamine and Opiate Dependence: Implications for Treatment. *Neuropsychol Rev*. 2007; 17: 317–336. DOI 10.1007/s11065-007-9033-y.
40. Ersche KD, Clark L, London M, Robbins TW, Sahakian BJ. Profile of executive and memory function associated with amphetamine and opiate dependence. *Neuropsychopharmacology*. 2006; 31, 1036–1047.
41. Faleh A Sawair, Ammar Al-Mutwakel, Kamal Al-Eryani, Ameera Al-Surhy, Satoshi Maruyama, Jun Cheng, Ali Al-Sharabi, Takashi Saku. High relative frequency of oral squamous cell carcinoma in Yemen: qat and tobacco chewing as its aetiological background. *International Journal of Environmental Health Research*. 2007; 17(3): 185-195.
42. Fasanmade A, Kwok E, Newman L. Oral squamous cell carcinoma associated with Khat chewing. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2007; 104(1): e53-5.
43. Flay BR, Petraitis J, Hu FB. Psychosocial risk and protective factors for adolescent tobacco use. *Nicotine Tobacco Research*. 1999; 1(Suppl 1): S59–65.
44. Frausto KA, Bazargan-Hejazi S. Who is Ready to Change Illicit Drug Use Behavior: An Emergency Department Study. *Substance Abuse: Research and Treatment*. 2009; 3: 53–60.
45. Gelaw Y, Haile-Amlak A. Khat chewing and its socio-demographic correlates among the staff of Jimma University. *Ethiop.J.Health Dev*. 2004; 18(3): 179-184 .
46. Galloway GP, Singleton EG. The Methamphetamine Treatment Project Corporate Authors. How long does craving predict use of methamphetamine? Assessment of use one to seven weeks after the assessment of craving. *Substance Abuse: Research and Treatment*. 2008; 1: 63–79.
47. Geissshusler S, Brenneisen R. The content of psychoactive phenylpropyl and phenylpentenyl Khatamines in *Catha edulis* Forsk. of different origin. *J Ethnopharmacol*. 1987; 19: 269-277.
48. Gelaw Y, Haile-Amlak A. Khat chewing and its socio-demographic correlates among the staff of Jimma University. *Ethiop.J.Health Dev*. 2004; 18(3): 179-184.
49. Getahun W, Gedif T, Fikru Tesfaye F. Regular Khat (*Catha edulis*) chewing is associated with elevated diastolic blood pressure among adults in Butajira, Ethiopia: A comparative study. *BMC Public Health* 2010; 10:390 doi:10.1186/1471-2458-10-390.
50. Gori G, Benowitz N, Lynch C. Mouth versus deep airways absorption of nicotine in cigarette smokers. *Pharmacol Biochem Behav*. 1986; 25: 1181-1184.
51. Griffiths P, Dominique L, Roumen S, Ana G, Brendan H, André N, Luis R. Khat use and monitoring drug use in Europe: The current situation and issues for the future. *Journal of Ethnopharmacology*. 2010; 132(3):578-583. doi:10.1016/j.jep.2010.04.046.
52. Gupta R, Prakash H, Gupta VP, Gupta KD. Prevalence and determinants of coronary health disease in a rural population in India. *J Clinl Epidemiol*. 1997; 50:203–9.
53. Halbach H. Medical aspects of the chewing of Khat leaves. *Bull World Health Organ*. 1972; 47(1): 21-9.
54. Han DH, Yoon SJ, Sung YH, Lee YS, Kee BS, Lyoo IK, et al. A preliminary study: novelty seeking, frontal executive function, and dopamine receptor (D2) Tag1 A gene polymorphism in patients with methamphetamine dependence. *Comprehensive Psychiatry*. 2000; 49: 387-392.
55. Hassan NA, Gunaid AA, Abdo-Rabbo AA, Abdel-Kader ZY, Al-Mansoob MA, Awad AY, Murray-Lyon IM. The effect of Qat chewing on blood pressure and heart rate in healthy volunteers. *Tropical Doctor*. 2000; 30(2): 107-108.
56. Health Officers Council of British Columbia, A Public Health Approach to Drug Control in Canada: Discussion Paper. Downloaded from: <http://www.cfdp.ca/bchoc.pdf>. 2005. (accessed on Tuesday 20 December 2011).
57. Henningfield JE, Keenan RM, Clarke PBS. Nicotine. In: Schuster CR, Kuhar M, eds. *Pharmacological aspects of drug dependence*. Berlin. 1996; Springer-Verlag: 272–314.
58. Hekmat S, Mehrjerdi ZA, Moradi A, Ekhtiari H, Bakhshi S. Cognitive Flexibility, Attention and Speed of Mental Processing in Opioid and methamphetamine Addicts in Comparison with Non-Addicts. *Neuroscience*. 2011; 2(2): 12-19.
59. Hoffman R, Al'bsi M. Khat use and neurobehavioral functions: Suggestions for future

- studies. *J Ethnopharmacol.* 2010; 132(3): 554–563. Doi:10.1016/j.jep.2010.05.033.
60. Humfleet GL, Haas AL. Is marijuana use becoming a 'gateway' to nicotine dependence? *Addiction.* 2004; 99(1):5–6. PMID: 14678052.
 61. Hurt RD, Patten CA. Treatment of tobacco dependence in alcoholics. *Recent Developments in Alcoholism.* 2003; 16: 335–359. PMID: 12638645.
 62. Jha P, Jacob B, Gajalakshmi V, Gupta PC, Dhingra N, Kumar R. A nationally representative case-control study of smoking and death in India. *N Engl JMed.* 2008; 358: 1137–47.
 63. John U, Meyer C, Rumpf H, Schumann A, Thyrian J, Hapke U. Strength of the relationship between tobacco smoking, nicotine dependence and the severity of alcohol dependence syndrome criteria in a population-based sample. *Alcohol and Alcoholism* 2003; 38(6): 606–612. PMID: 14633650.
 64. Kalix P, Geissshusler S, Brenneisen R, Koelbing U, Fisch HU. Cathinone, a phenylpropylamine alkaloid from Khat leaves that has amphetamine effects in humans. *NIDA Res. Monogr.* 1990; 105: 289–290.
 65. Kalix P, Braenden O. Pharmacological aspects of the chewing of Khat leaves. *Pharmacol Rev.* 1985; 37(2): 149-64.
 66. Kalix P. Khat: a plant with amphetamine effects. *Journal of Substance Abuse and Treatment.* 1988; 5: 163–169.
 67. Kalix P. Cathinone a natural amphetamine. *Pharmacology and Toxicology.* 1992; 70: 77–86.
 68. Kenny PJ, Markou A. Neurobiology of the nicotine withdrawal syndrome. *Pharmacology, Biochemistry and Behavior.* 2001; 70: 531–549.
 69. Kennedy JG. *The flower of paradise: the institutionalized use of the drug qat in North Yemen.* D. Reidel Publishing Company, The Netherlands. 1987.
 70. Khan A, Malhotra D. Protective Role of Ascorbic Acid (Vitamin C) Against Hyperlipidemia and Enhanced Oxidizability of Low Density Lipoprotein in Young Smokers. *European Journal of Experimental Biology.* 2011; 1 (1): 1-9.
 71. Kobus K. Peers and adolescent smoking. *Addiction.* 2003; 98(Suppl 1): 37–55.
 72. Köseoğlu N, Aydın A, Uçan ES, Ceylan E, Eminoğlu O, Durak H, Güven H. The effects of water-pipe, cigarette and passive smoking on mucociliary clearance. *Tuberk Toraks.* 2006; 54(3): 222-8. PMID:17001538.
 73. Lai S, Lai H, Page JB, McCoy CB. The association between cigarette smoking and drug abuse in the United States. *Journal of Addictive Diseases.* 2000; 19(4): 11–24. PMID: 11110061.
 74. Lamina, S. Khat (*Catha edulis*): The herb with officio-legal, socio-cultural and economic uncertainty. *S Afr J Sci.* 2010; 106(3/4): 1- 4.
 75. Laswar AK, Darwish H. Prevalence of cigarette smoking and Khat chewing among Aden university medical students and their relationship to BP and body mass index. *Saudi J Kidney Dis Transpl.* 2009; 20(5): 862-6. Available from: <http://www.sjkdt.org/text.asp?2009/20/5/862/5538>
 76. Lukandu OM, Neppelberg E, Vintermyr OK, Johannessen AC, Costea DE. Khat Alters the Phenotype of *in vitro*-reconstructed Human Oral Mucosa. *J Dent Res.* 2010; 89(3): 270-275. DOI: 10.1177/0022034509354980.
 77. Lukandu OM, Costea EA, Neppelberg E, Bredholt T, Gjertsen BT, Johannessen C, Vintermyr, OK. Early loss of mitochondrial membrane potential in cell eath induced by Khat in primary normal oral cells. *Toxicology.* 2009; 263(2-3): 108-116. DOI: 10.1016/j.tox.2009.06.024.
 78. Lukandu OM, Costea DE, Dimba EA, Neppelberg E, Bredholt T, Gjertsen BT, Vintermyr O K, Johannessen AC. Khat induces G1-phase arrest and increased expression of stress-sensitive p53 and p16 proteins in normal human oral keratinocytes and fibroblasts. *Eur J Oral Sci,* 2008a; 116(1): 23-30. PMID:18186728.
 79. Lukandu OM, Costea DE, Neppelberg E, Johannessen AC, Vintermyr OK. Khat (*Catha edulis*) induces reactive oxygen species and apoptosis in normal human oral keratinocytes and fibroblasts. *Tox Sci,* 2008b; 103(2): 311-324. doi: 10.1093/toxsci/kfn044.
 80. Magura S, Rosenblum A, Betzler T. Substance Use and Mental Health Outcomes for Comorbid Patients in Psychiatric Day Treatment. *Substance Abuse: Research and Treatment.* 2009; 3: 71–78.
 81. Mahmoud A Alabdalla. Chemical characterization of counterfeit captagon tablets seized in Jordan. *Forensic Sci Int.* 2005; 152(2-3): 185-8. doi:10.1016/j.forsciint.2004.08.004.
 82. Malin DH. Nicotine dependence studies with a laboratory model. *Pharmacology, Biochemistry and Behavior.* 2001; 70: 551–559.
 83. Malson J, Lee E, Murty R, Murty R, Moolchan ET, Pickworth WB. Clove cigarette smoking: biochemical, physiological and subjective effects. *Pharmacol Biochem Behav.* 2003; 74(3): 739-745.
 84. Mion G, Oberti M, Ali A W. Hypertensive effects of qat. *Médecine tropicale revue du Corps de sante colonial.* 1998; 58(3): 266-268.
 85. Maziak, W. 2011. The global epidemic of waterpipe smoking. *Addict. Behav.,* 36: 1–5.
 86. Murdoch C, Hesham A, Hsin-Yu F, Hussun J, Raga M, Munitta M. Khat (*Catha edulis*) alters the

- phenotype and anti-microbial activity of peripheral blood mononuclear cells. *Journal of Ethnopharmacology*. 2011; 138(3): 780-787. doi:10.1016/j.jep.2011.10.030.
87. Nageeb AG, Abdallah A Gunaid, Fouad M Y El Khally, Iain M Murray-Lyon. The subjective effects of chewing Qat leaves in human volunteers. *Annals of Saudi Medicine*. 2002; 22(1-2): 34-37.
 88. Nutt David, Leslie A King, William Saulsbury, Colin Blakemore. Development of a rational scale to assess the harm of drugs of potential misuse. *The Lancet*. 2007; 369: 1047-1053.
 89. Odenwald M. Chronic Khat use and psychotic disorders: a review of the literature and future prospects. *Sucht*. 2007; 53: 9-22.
 90. Odenwald M, Hinkel H, Schauer E, Neuner F, Schauer M, Elbert T. The consumption of Khat and other drugs in Somali combatants: a cross-sectional study. *PLoS Medicine*. 2007; 4: 1959-1972.
 91. Odenwald M, Hinkel H, Schauer E, Schauer M, Elbert T, Neuner F, Rockstroh B. Use of Khat and posttraumatic stress disorder as risk factors for psychotic symptoms: a study of Somali combatants. *Social Science & Medicine*. 2009; 69: 1040-1048.
 92. Odenwald M, Neuner F, Schauer M, Elbert T, Catani C, Lingenfelter B, Hinkel H, Hafner H, Rockstroh B. Khat use as risk factor for psychotic disorders: a cross-sectional and case-control study in Somalia. *BMC Medicine*. 2005; 3: 5-15.
 93. Pasupathi P, Bakthavathsalam G, Yagneswara YR, Farook J. Cigarette smoking—Effect of metabolic health risk: A review. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*. 2009; 3: 120-127. doi:10.1016/j.dsx.2009.02.006.
 94. Paterson D, Nordberg A. Neuronal nicotinic receptors in the human brain. *Progress in Neurobiology*. 2000; 61:75-111.
 95. Pennings EJM, Opperhuizen A, van Amsterdam JGC. Risk assessment of Khat use in the Netherlands: A review based on adverse health effects, prevalence, criminal involvement and public order. *Regulatory Toxicology and Pharmacology*. 2008; 52(3): 199-207. doi:10.1016/j.yrtph.2008.08.005.
 96. Rani M, Bonu S, Jha P, Nguyen SN, Jamjoum L. Tobacco use in India: prevalence and predictors of smoking and chewing in a national cross sectional household survey. *Tobacco Control*. 2003;12: e4-e4. www.tobaccocontrol.com/cgi/content/full/12/4/e4.
 97. Rashad Elsanosi, Bani I, Ageely H.,Milaat, W, El-Najjar, M, Makeen A, and Umar Yagob. *Socio-medical problem of the habituation of Khat chewing in Jazan Region in Southern Saudi Arabia*. *European Journal of Scientific Research*. 2011; 63(1): 122-133.
 98. Reda A, Moges A, Biadgilign S, Wondmagegn BY. Prevalence and Determinants of Khat (*Catha edulis*) Chewing among High School Students in Eastern Ethiopia: A Cross-Sectional Study. *PLoS ONE*, 2012; 7(3): e33946. doi:10.1371/journal.pone.0033946.
 99. Reno F, Rocchetti, P, Migliario M, Rizzi M, Cannas M. Chronic exposure to cigarette smoke increases matrix metalloproteinases and Filaggrin mRNA expression in oral keratinocytes: Role of nicotine stimulation. *Oral Oncology*. 2011; 47: 827-830. doi:10.1016/j.oraloncology.2011.06.006.
 100. Rogers RD, Robbins TW. *The neuropsychology of chronic drug abuse*. In: Ron MA, Robbins TW (eds). Disorders of Brain and Mind. Cambridge University Press: Cambridge. 2003.
 101. Roskin J and Aveyard P. Canadian and English students' beliefs about waterpipe smoking: a qualitative study. *BMC Public Health*. 2009; 9: 10. doi: 10.1186/1471-2458-9-10.
 102. Royal College of Physicians. *Harm reduction in nicotine addiction: helping people who can't quit*. A report by the Tobacco Advisory Group of the Royal College of Physicians. London: RCP. 2007.
 103. Rastam S, Fu-Min L, Fouad MF, Haysam M Al Kamal, Nizar Akil, Ala-Eddin Al Moustafa. Water pipe smoking and human oral cancers. *Medical Hypotheses*. 2010; 74(3): 457-459.
 104. Schoenmaker N, Hermanides J and Davey G. Prevalence and predictors of smoking in Butajira town, Ethiopia. *Ethiop.J.Health Dev*. 2005; 19(3): 182-187.
 105. Sharma G and Vijayaraghavan S. Nicotinic Receptors: Role in Addiction and Other Disorders of the Brain. *Substance Abuse: Research and Treatment*. 2008; 1: 81-95.
 106. Shatoor AS, Mahfouz AA, Khan MY, Daffalla, AA, Mostafa O. and Hammad RK. Cardiovascular Risk Factors among Adolescent Secondary School Boys in Ahad Rufeida, Southwestern Saudi Arabia. *Journal of Tropical Pediatrics*. 2011; 57(5): 382-384. doi:10.1093/tropej/fmq108.
 107. Silber B, Croft R, Papafotiou K, Stough C. The acute effects of d-amphetamine and methamphetamine on attention and psychomotor performance. *Psychopharmacology (Berlin)*. 2006; 187(2):154-169. PMID:16761129.
 108. Smith SY. *Nicotine product harm perception and psychosocial correlates of use in college freshmen*. Baltimore: The Johns Hopkins University. 2006.
 109. Smith CJ, Perfetti TA, Rumble MA, Rodgman A, Doolittle DJ. "IARC group 2A Carcinogens" reported in cigarette mainstream smoke. *Food Chem Toxicol*. 2000; 38(4): 371-83.

110. Smith CJ, Livingston SD, Doolittle DJ. An international literature survey of "IARC Group I carcinogens" reported in mainstream cigarette smoke. *Food Chem Toxicol.* 1997; 35(10–11): 1107–30.
111. Smith-Simone SY, Curbow BA and Stillman FA. Differing psychosocial risk profiles of college freshmen waterpipe, cigar, and cigarette smokers. *Addictive Behaviors.* 2008; 33: 1619–1624. doi:10.1016/j.addbeh.2008.07.017.
112. Smith-Simone S, Maziak W, Ward KD and Eissenberg T. Waterpipe tobacco smoking: Knowledge, attitudes, beliefs, and behavior in two U.S. samples. *Nicotine Tobacco Research.* 2008; 10(2): 393–398.
113. Sohn M, Hartley C, Froelicher E, and Benwitz NL. Tobacco use and dependence. *Seminars in Oncology Nursing.* 2003; 19(4): 250-260.
114. Sutfin EL, McCoy, TP, Reboussin, BA, Wagoner, KG, Spangler, J, Wolfson M. Prevalence and correlates of waterpipe tobacco smoking by college students in North Carolina. *Drug and Alcohol Dependence.* 2011; 115(1-2): 131-136. doi:10.1016/j.drugalcdep.2011.01.018.
115. Tariq A. Al-Habeeb and Naseem A. Qureshi. Smoking among male psychiatric outpatients in Saudi Arabia. *Annals of Saudi Medicine.* 2000; 20(3-4): 218-223.
116. Tesfaye F, Byass P, Wall S, Berhane Y, Bonita R. Association of smoking and Khat (*Catha edulis* Forsk) use with high blood pressure among adults in Addis Ababa, Ethiopia 2006. *Prev Chronic Dis.* 2008; 5(3):A89. PMID:18558039.
117. Tobacco.org. Additive-free, candy-flavoured cigarettes toxic as regulars. Available at: <http://www.tobacco.org/news/110380.html>. 2011. (last updated Tues 19 Dec 2011).
118. Toennes SW, Harder S, Schramm M, Niess C, Kauert GF. Pharmacokinetics of cathinone, cathine and norephedrine after the chewing of Khat leaves. *Br J Clin Pharmacol.* 2003; 56(1): 125-30.
119. Tomar SL and Asma S. Smoking-attributable periodontitis in the United States: findings from NHANES III. National Health and Nutrition Examination Survey. *J. Periodontol.* 2000;71(5): 743–51.
120. TMCDDA. *National Report to the EMCDDA by the Reitox National Focal Point.* Turkish Monitoring Center for Addiction and Drugs Addiction. Available at: http://www.tubim.gov.tr/Dosyalar/RAPORLAR/2008_turkiye_rapor_en.pdf. 2008. (accessed on 5 Dec 2011).
121. Verdejo-Garcia A, Lopez-Torrecillas F, Gimenez CO, and Perez-Garcia M. Clinical implications and methodological challenges in the study of the neuropsychological correlates of cannabis, stimulant, and opioid abuse. *Neuropsychology Review.* 2004; 14: 1-41.
122. Vidal C. Nicotinic receptors in the brain: molecular biology, function, and therapeutics. *Molecular Chemistry and Neuropathology.* 1996; 28: 3–11.
123. United Nations. World Population Prospects: Revision of 2004. Report No. ESA/P/WP.193. New York. Downloaded from: http://www.un.org/esa/population/publications/WP/P2004/2004Highlights_finalrevised.pdf. 2005. (accessed on 21 December 2011).
124. UNODC (United Nations Office on Drugs and Crime). *World Drugs Report.* United Nations Publication Sales No. E.09.XI.12. UN, New York. 2009.
125. UNODC (United Nations Office on Drugs and Crime). *Statistics on drug trafficking trends in the Near and Middle East, in South, West and Central Asia and worldwide.* Report No. UNODC/SUBCOM/45/2. 2010.
126. US Department of Health and Human Services. *The health consequences of smoking: Nicotine addiction.* A Report of the Surgeon General. Rockville, MD, US Department of Health and Human Services Publication.1988.
127. WHO. Substance Abuse. Available at: http://www.who.int/topics/substance_abuse/en/. 2011. (Accessed on Tuesday 20 December 2011).
128. WHO (World Health Organization). Study Group on Tobacco Product Regulation (TOBREG), Waterpipe Tobacco Smoking: Health Effects, Research Needs and Recommended Action by Regulators, WHO, Geneva. 2005.
129. WHO (World Health Organization). *Neuroscience of psychoactive substance use and dependence.* World Health Organization. Report No ISBN 92 4 156235 8 (LC/NLM classification: WM 270). Geneva, Switzerland. 2004.
130. WHO (World Health Organization). *Lexicon of alcohol and drug terms.* Geneva, Switzerland, World Health Organization. 1994.
131. Yen CF, Wu HY, Yen JY, and Ko CH. Effects of brief cognitive-behavioral interventions on confidence to resist the urges to use heroin and methamphetamine in relapse-related situations. *J. Nerv. Ment. Dis.* 2004; 192(11): 788–91.
132. Zein ZA. Polydrug abuse among Ethiopian university students with particular reference to Khat (*Catha edulis*). *J Trop Med Hyg.* 1988; 91(2): 71-5.

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